Project Title: PROmotion of FLU Vaccine uptake in the Emergency Department – PROFLUVAXED

R01 AI166967-01

Sub-study: RTC for flu vaccine messaging platforms

Date of Document: September 16, 2022

Study Procedures Manual for PROFLUVAXED – A 3-arm Cluster Randomized Trial:

Contents

Overview

This PROmotion of inFLUenza VAX(ccine) in the Emergency Department PROFLUVAXED MOP is a sub-study and extension of the PROCOVAXED trial. The PROCOVAXED trial is a multicenter study that seeks to decrease COVID-19 vaccine hesitancy and increase COVID-19 vaccine uptake through the use of vaccine messaging platforms in the emergency department (ED). In this trial we found that implementation of our COVID-19 messaging platforms (videos, information sheets and scripted, direct messaging) was associated with greater COVID-19 vaccine acceptance and uptake in unvaccinated ED patients. (primary manuscript currently under review).

Other aims for our PROCOVAXED NIAID Grant R01 AI166967-01 included the similar development and testing of influenza vaccine messaging platforms. Toward this influenza vaccine aim, we conducted multiple in-depth qualitative interviews with ED patients whose primary health care access is the ED. During these interviews we queried about flu vaccine access and reasons for hesitancy. We have reviewed these interviews in detail and developed 5 PROFLUVAXED messaging videos, 5 flyers and a scripted message to be used in this trial. In this PROFLUVAXED sub-study of PROCOVAXED, we seek to address the specific aims below. Of note, while the general procedures and analysis closely mirror the PROCOVAXED study, we have adapted this protocol in response to notable findings and limitations in the parent PROCOVAXED study, as well as specifics about influenza vaccination, which only occurs during limited periods of the year.

In our PROCOVAXED trial we noted that approximately 10% of patients who did **not** receive COVID-19 vaccine messaging agreed to receive the COVID-19 vaccine when questioned in the ED and 8% received the COVID-19 vaccine at 30 days, leading the investigator team to believe that merely asking patients whether or not they will accept vaccines (without any messaging) in the ED and informing their ED providers when they say they would accept it **is an intervention unto itself** that can lead to greater vaccine uptake. We intend to test that hypothesis in Specific Aim III of this PROFLUVAXED trial by adding a third arm in which participants will not be asked whether they would accept the influenza vaccine in the ED (and correspondingly, research staff will not inform ED providers that the participant would accept the influenza vaccine). This third arm will allow us to determine whether the intervention of asking patients whether they would accept an influenza vaccine in the ED increases vaccine uptake. It will also allow us to dissect reasons for success (or failure) of the primary intervention (vaccine messaging), and refine recommendations about vaccine messaging programs accordingly. This third study arm may also allow the study team to discern which of the two primary intervention components (the vaccine messaging vs the asking of the vaccine acceptance question and informing providers) has the greatest effect (or lack of effect) on influenza vaccine uptake.

Because of Omicron variant associated surges during the COVID-19 pandemic with corresponding research staff illness and ED overcrowding, we also found wide week-to-week fluctuations in enrollment in the PROCOVAXED study. To reduce this variability of enrollment, we have changed the unit of randomization from 1-week to 1-day. We also found that the vast majority of participants who received the COVID-19 vaccine in the study received it in the ED, rather than elsewhere after their ED visit. We therefore are making the primary outcome of this study influenza vaccine uptake in the ED, instead of vaccine uptake at 30 days post-ED visit. We seek to accomplish the following specific aims:

Specific Aim I: To determine whether implementation of influenza vaccine trusted messaging platforms is associated with increased influenza vaccine uptake in unvaccinated ED patients.

At six EDs (Zuckerberg San Francisco General, UCSF Parnassus Medical Center [San Francisco, CA], Thomas Jefferson University Hospital [Philadelphia, PA], Ben Taub Hospital [Houston, TX], Harborview Medical Center [Seattle, WA], and Duke University Medical Center [Durham, NC]), we will conduct a cluster-randomized controlled trial of implementation of PROFLUVAXED trusted messaging platforms, with influenza vaccine uptake in the ED as the primary outcome. *Hypothesis: Implementation of PROFLUVAXED trusted messaging platforms in EDs will be associated with increased influenza vaccine uptake in unvaccinated ED patients.*

Specific Aim II: To determine whether implementation of influenza vaccine trusted messaging platforms in EDs is associated with increased influenza vaccine acceptance in unvaccinated ED patients. For this specific aim influenza vaccine acceptance in the ED assessed via ED survey will be the primary outcome. *Hypothesis: Implementation of PROFLUVAXED trusted messaging platforms in EDs will be associated with increased influenza vaccine acceptance in unvaccinated ED patients.*

Specific Aim III: To determine whether implementation of a protocol in which ED patients are asked whether they will accept an influenza vaccine in the ED (and notifying ED providers when they say they will accept it) is associated with increased influenza vaccine uptake in unvaccinated ED patients. *Hypothesis: Implementation of an ED protocol in which patients are asked whether they will accept an influenza vaccine (and notifying ED providers when they say they will accept it) will be associated with increased influenza vaccine uptake in unvaccinated ED patients.*

General Design: This is a three-arm cluster-randomized controlled trial (CRCT) to accomplish Specific Aims I, II and III.

Study arms

PROFLUVAXED Intervention M arm (Messaging and Vaccine Question)	Intervention Q arm (Vaccine Question, but No Messaging)	Control arm (No Messaging, No Vaccine Acceptance Question)
• Vaccine messaging given • Vaccine acceptance question asked	• No vaccine messaging • Vaccine acceptance question asked	• No vaccine messaging • No vaccine acceptance question

Primary Outcome for Specific Aims I and III

Influenza vaccine Uptake in the ED

The primary outcome for Specific Aims I and III is **Influenza Vaccine Uptake** in the ED, which will be ascertained by direct query of study participants, their ED providers and review of ED electronic health records. For Specific Aim I, this primary outcome will be compared between the Intervention M arm (Messaging and vaccine acceptance) and the Control arm (No messaging, no vaccine acceptance question). For Specific Aim III, this primary outcome will be compared between the Intervention Q arm (Vaccine question but no messaging) and the Control arm (No messaging, no vaccine acceptance question).

Primary Outcome for Specific Aim II

The primary outcome of Specific Aim II is **Influenza Vaccine Acceptance** in the ED, which will be ascertained by a survey question of study participants in the ED. This outcome will be compared between the Intervention M arm (Messaging and vaccine acceptance) and the Intervention Q arm (Vaccine question but no messaging).

I. IRB

We will submit our protocol to the UCSF Committee on Human Research as a modification. We will continue with multi-site reliance mechanism for the PROCOVAXED study as per NIH guidelines for randomized trials.

II. Deposition of Protocol into ClinicalTrials.Gov

As per federal regulations, we will deposit our full study protocol into the repository https://clinicaltrials.gov/

Setting and Sites

We will conduct this over 5 and a half months (mid-September 2022 to February 28, 2023) at six high-volume EDs in five cities: (Zuckerberg San Francisco General, UCSF Parnassus Medical Center [San Francisco, CA], Thomas Jefferson University Hospital [Philadelphia, PA], Ben Taub Hospital [Houston, TX], Harborview Medical Center [Seattle, WA], and Duke University Medical Center [Durham, NC]). We have chosen this time-period to coincide with the influenza vaccination season.

Unit of Randomization

Sites will be assigned be assigned to a condition for a day. Randomization within each of the site uses pseudorandom number to permute blocks of time. The blocks consist of 15 days duration during which each condition appears for 5 days. Hence, in any 15 day period there will be a balance of interventions within each of the sites. The particular days of each week (Monday, Tuesday, Wednesday, Thursday and Friday) for each of the study arms will thus vary randomly. This randomization scheme will minimize secular trends (changes in perceptions about the flu vaccine that may occur through the course of the influenza vaccine season). We will generate a full study calendar based on this randomization scheme. To try to maintain masking of allocation, sites will be given a blacked out study calendar and will be instructed to open the calendar for a particular study day the morning of that study day (other than that study day, the rest of the calendar will remain blacked out).

Site Orientation and Training

The Core UCSF Site will develop orientation materials to familiarize the ED Sites with the study protocol. Each site will employ one or more Clinical Research Coordinators (CRCs), who will report to the Site PI and be responsible for day-to-day study implementation. We will develop and disseminate a manual of operating procedures (MOP) with standard personnel training methods, including education kits with scripts, summary cards, and PowerPoint presentations to assist coordinators in the orientation of site clinicians and other staff to our study protocol. We will convene ZOOM conference calls to review this summary and develop plans for optimization of PROFLUVAXED messaging platforms to improve usability and workflow. We will refine procedures with updates delivered to the site PIs during weekly ZOOM conferences.

Study Hotline and Quality Assurance

We will maintain a study hotline and encourage study personnel to contact the PI and Central Study Coordinator for all issues and queries. Hotline hours will be during primary study hours (weekday 8 a.m. to 5 p.m. PST).

We will enact rigorous methods for clinical trial quality assurance and performance improvement, including: 1) systematic review of enrollment logs, 2) weekly audits of random samples of data for accuracy and missing elements, and 3) structured review of protocol deviations or violations. The Central Study Coordinator will prepare monthly summary report cards, tabulating individual site quality assurance metrics for review during scheduled Steering Committee calls. The overall study PI (Dr. Rodriguez) will discuss site-specific data with site PIs individually and summarize these data collectively during Steering Committee calls, with prompt dissemination of plans for process improvement.

Recruitment, Inclusions, Exclusions and Consent

Practical budget considerations and limits on research personnel in patient care areas during the COVID-19 pandemic, preclude 24/7 delivery of the PROFLUVAXED trusted messaging platforms and enrollment in this study. We will use a convenience sample technique to approach all eligible adult patients who present to our study EDs during 8-hour (one-day) blocks, typically beginning at approximately 9 a.m. and continuing to approximately 5 pm. Sites will be given leeway to vary their particular study time hours, as long as these study hours remain consistent from week to week.

Inclusions will be:

1) Adults
2) Presenting to ED
3) Not already vaccinated for influenza in the current year
4) Able to provide informed consent
5) Fluent in English or Spanish
6) Anticipated ability to complete study intervention in ED i.e., able to watch a 3-minute videoclip

Reviewing ED triage information, we will exclude patients with the following characteristics:

1) Age < 18 years

2) Major trauma such that it will preclude survey

3) Inability to participate in a survey because of intoxication, altered mental status, or critical illness

4) Incarceration

5) Psychiatric hold

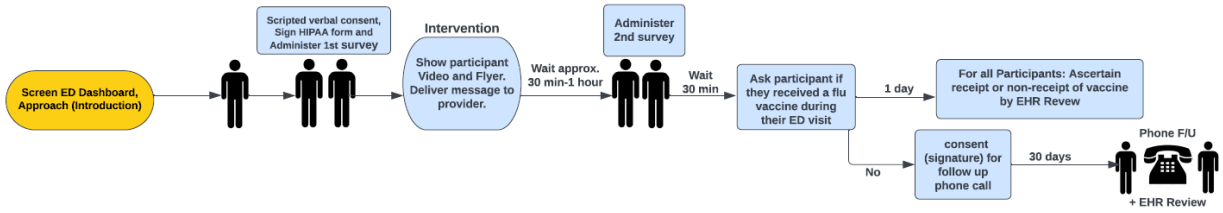
6) We will also exclude patients who state that they have already received an influenza vaccine and patients who are in the ED for suspected acute Covid or influenza illness.

NOTE: For all 3 study arms, study procedures should be performed in patient waiting times and not interfere or disrupt patient care in any way.

Procedures and workflow during PROFLUVAXED Intervention M study arm

The anticipated flow of the study during the Intervention M study blocks is summarized in Figure 1. CRCs and research personnel will begin by setting up their home base of Consents and platforms (video clips, printed materials and scripts for messaging).

Figure 1: Intervention M Arm Study Flow



Introduction to ED Staff: Clinical Research Coordinators (CRCs) will set up their workstation in the ED and introduce themselves to ED staff (nurses, physicians and mid-levels), informing them that they will be doing the PROFLUVAXED study that day. **They will avoid telling providers whether this is an intervention vs control arm.**

Initial Screening and Scripted Consent for Surveys: CRCs will review ED dashboards for inclusion and exclusion information. When an eligible patient is identified, the CRC will ask the nurse or doctor caring for the patient whether it is Ok for them to approach the patient about the study. For provider approved patients: CRCs will approach eligible patients and deliver a scripted consent for two short surveys (Pre-intervention) Intake Survey and the (Post-Intervention) Vaccine Acceptance Survey. See Scripted Consent for the Intervention period. **They will also get written HIPAA authorization for review of their ED EHR. If the patient does not agree to this HIPAA review of their EHR, they will be excluded from the study.** Participants will not be compensated for participation.

CRCs will complete screening and enrollment log indicating whether or not they agreed to participate. If they agreed to participate, the CRC will assign a Study ID#.

Intake Survey: We will administer the INTAKE SURVEY to participants. CRCs will have the option of inputting surveys to REDCap on iPads in real time or using paper surveys (and later inputting into REDCap). These surveys are to be delivered orally (CRC asks questions), not via handing them out. The Intake Surveys are the same for all three arms of the study.

Intervention M (messaging): The intervention will consist of three messaging platforms that were developed specifically to reduce influenza vaccine hesitancy. All platforms have been reviewed by the UCSF Committee on Human Research.

1) Video clips – short (approximately 3-minute) Public Service Announcement type videos to be shown to the participant on an iPad.
2) Printed materials – one page information sheets handed to subjects by CRCs.

3) Face to face messaging – short (< 1 minute), scripted message from the patient's providers in the ED (nurse or provider)

Each site will maintain a library of
A. 5 versions of the videos - the version used in any participant will be tailored to that participant's stated race/ethnicity. See ***below
B. 5 versions of printed flyers – likewise, the version will be tailored to the participant's stated race/ethnicity. See ***below
C. 1 version of scripted message to be delivered in English or Spanish.

Influenza Vaccine Flyer, Videos and Telling Provider to Deliver Message:

Interventions will be delivered in real-time patient visits in site EDs, during waiting times such that they will not interfere with patient care. At the end of the survey, the CRC will deliver the influenza vaccine information flyer and ask the patient if they will watch a short video about influenza vaccines. If they agree to watch the video, the CRC will give show them video on the iPad. After finishing with the video, the CRC will tell the subject that they will be back in about an hour for the Vaccine Acceptance survey. The CRC will then leave the room and ask the patient's primary provider (doctor, mid-level practitioner, or nurse) to deliver the influenza vaccine message (hand them the scripted message). This message is short and should not significantly impact provider workflow. Notably, vaccine messaging is recommended in the ED by the American College of Emergency Physicians and other health care organizations (Centers for Disease Control).

***We will deliver messaging from our platform libraries in patients' preferred language (English, Spanish). To the extent possible, we will follow recommendations to choose platforms from site libraries that match video clip and printed material messengers with subjects' likely preferences for race, ethnicity, age and gender (e.g., Latinx messenger on video clip with Latinx participant).

Vaccine Acceptance Survey (Post-Intervention) in the ED: We will administer the Vaccine Acceptance Survey: INTERVENTION GROUP at some time (generally 30 minutes but up to 3 hours) after the Intake Survey.

Primary and Other Outcome Ascertainment: Primary outcome ascertainment of influenza vaccination in the ED will occur by 2 methods:

1) Direct questioning of participants and their providers in the ED: Research staff will ask participants and their ED providers whether or not the participant received an influenza vaccine in the ED one hour but up to 6-hours after the Vaccine Acceptance Survey. Notably, ED patient visits are variable such that not all patients have stays lasting greater than an hour and a half. Research staff should endeavor to complete this ascertainment prior to discharge, even if that ascertainment occurs before an hour after the Vaccine Acceptance survey.

2) Review of each participant's ED EHR by research staff on the next workday after their index ED visit to confirm receipt (or non-receipt) of an influenza vaccine in the ED. **This EHR review will be conducted in a blinded fashion – the research staff person reviewing the EHR will be unaware of participant's study group assignment.**

Secondary outcome ascertainment of 30-day uptake of influenza vaccine will occur in three ways:

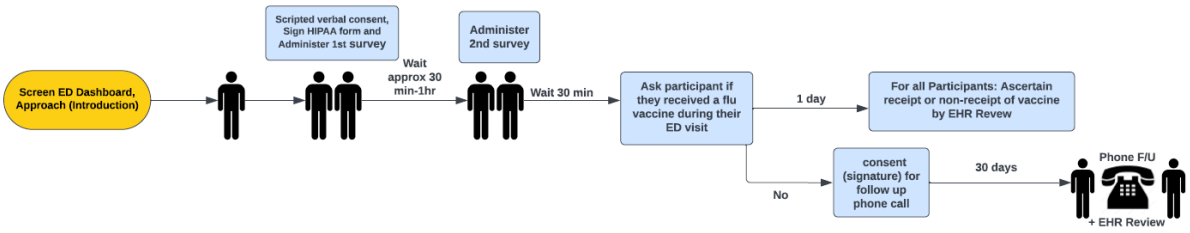
1) Ascertainment of vaccination in the ED as above by direct questioning and review of EHR records.
2) Blinded review of EHR at 30-days
3) For participants who have not received an influenza vaccine upon questioning in the ED, staff will ask whether they will agree to phone follow-up at 30 days. For those agreeing to follow-up, we will obtain written consent for phone follow-up (phone follow-up consent form). We will then ask participants for their best phone number(s) to reach them for a follow-up phone call. Sites will maintain a separate password protected database of subject IDs and follow up phone #s.

This method will assure that all study participants, even those who refuse phone follow-up, will have at least 2 ways of 30-day study outcome ascertainment (1 and 2 above).

Procedures and workflow during Intervention Q: (Vaccine Question, but No Vaccine Messaging)

The workflow during this arm is identical to the Intervention M Arm except there will be no messaging platforms delivered. The anticipated flow of the study during **Intervention Q Blocks** is summarized in Figure 2.

Figure 2: Intervention Q Arm Study Flow



Introduction to ED Staff: Clinical Research Coordinators (CRCs) will set up their workstation in the ED and introduce themselves to ED staff (nurses, physicians and mid-levels), informing them that they will be doing the PROFLUVAXED study that day. **They will avoid telling providers whether this is an intervention vs control arm.**

Initial Screening and Scripted Consent for Surveys: CRCs will review ED dashboards for inclusion and exclusion information. When an eligible patient is identified, the CRC will ask the nurse or doctor caring for the patient whether it is Ok for them to approach the patient about the study. For provider approved patients: CRCs will approach eligible patients and deliver a scripted consent for two short surveys – the Intake Survey and the (Post-Intervention) Vaccine Acceptance Survey. See Scripted Consent for the No Messaging arm period.

CRCs will complete screening and enrollment log indicating whether or not they agreed to participate. If they agreed to participate, the CRC will assign a Study ID#.

Intake Survey: We will administer the INTAKE SURVEY to participants. CRCs will have the option of inputting surveys to REDCap on iPads in real time or using paper surveys (and later inputting into REDCap). These surveys are to be delivered orally (CRC asks questions), not via handing them out. The Intake Surveys are the same for all three arms of the study.

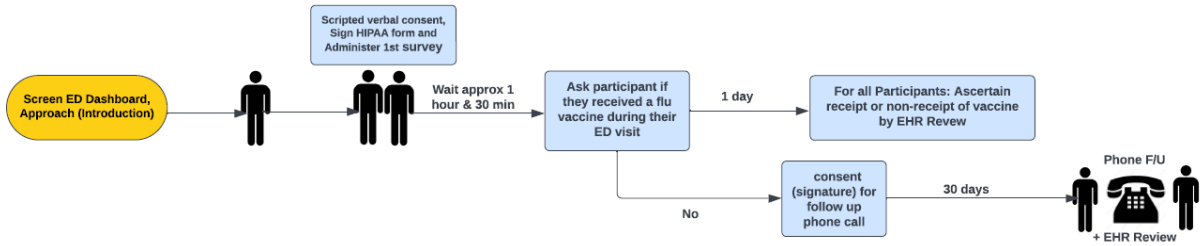
Vaccine Acceptance Survey: We will administer the Vaccine Acceptance Survey at some time (generally 30 minutes but up to 3 hours) after the Intake Survey. These surveys in the control group retain the same key primary and secondary outcome questions as in the intervention group Vaccine Acceptance surveys. See Vaccine Acceptance Survey: No Messaging arm.

Primary and Other Outcome Ascertainment: Ascertainment of primary and secondary outcomes will occur in the same manner as in the Intervention M arm.

Procedures and workflow during Control Arm: No Messaging, No Vaccine Acceptance Question Arm

The workflow during this arm is identical to the Intervention Q arm, except there will be no Vaccine Acceptance Question Survey. The anticipated flow of the study during **Control Blocks** is summarized in Figure 3.

Figure 3: Control Arm Study Flow



Introduction to ED Staff: Clinical Research Coordinators (CRCs) will set up their workstation in the ED and introduce themselves to ED staff (nurses, physicians and mid-levels), informing them that they will be doing the PROFLUVAXED study that day. **They will avoid telling providers whether this is an intervention vs control arm.**

Initial Screening and Scripted Consent for Surveys: CRCs will review ED dashboards for inclusion and exclusion information. When an eligible patient is identified, the CRC will ask the nurse or doctor caring for the patient whether it is Ok for them to approach the patient about the study. For provider approved patients: CRCs will approach eligible patients and deliver a scripted consent for two short surveys – the Intake Survey and the (Post-Intervention) Vaccine Acceptance Survey. See Scripted Consent for the No Messaging, No Vaccine Acceptance Question arm period.

CRCs will complete screening and enrollment log indicating whether or not they agreed to participate. If they agreed to participate, the CRC will assign a Study ID#.

Intake Survey: We will administer the INTAKE SURVEY to participants. CRCs will have the option of inputting surveys to REDCap on iPads in real time or using paper surveys (and later inputting into REDCap). These surveys are to be delivered orally (CRC asks questions), not via handing them out. The Intake Surveys are the same for all three arms of the study.

Primary and Other Outcome Ascertainment: Ascertainment of primary and secondary outcomes will occur in the same manner as in the Intervention arms.

Research staff informing ED providers when participants will accept Influenza vaccine for Intervention M and Intervention Q arms

Our study site EDs will usually have the capability of administering Influenza vaccines, and we expect that this will continue for the duration of the trial. The last question in the Vaccine Acceptance Survey **in both the Intervention M and Intervention Q arms** of the study is "*Would you accept the flu vaccine in the emergency department today if your doctor asked you?*" When a participant says they will accept the vaccine, the CRC or research staff will ask the participant if it is OK to notify that participant's ED provider(s) – nurse and/or physician that they said they will accept the vaccine and confirm whether or not they receive it in the ED. Research staff will not tell patients that they qualify for the flu vaccine and will not advise them in any manner. When participants agree to notification of the ED provider, research staff will notify the ED provider that they stated they will accept the vaccine. They will not tell the provider that they meet criteria for the influenza vaccine and will not push that they get vaccinated.

Primary Outcome and Ascertainment of Specific Aim I

Our primary outcome for Specific Aim I is influenza vaccination uptake in the ED, **comparing the Intervention M arm vs the Control (No Messaging and No Vaccine Acceptance Question) arm**.

Primary and Other Outcome Ascertainment: Primary outcome ascertainment will occur by review of each participant's ED EHR by research staff on the next workday after their index ED visit. Staff will check the EHR to confirm receipt (or non-receipt) of an influenza vaccine in the ED. This review will be conducted in a blinded fashion – the research staff person reviewing the EHR will be unaware of participant's study group assignment.

Participants who have confirmed receipt by EHR review will be deemed "vaccinated in the ED". Conversely, participants who do not have confirmed receipt by review will be deemed to be "not vaccinated in the ED"

Our secondary outcome for Specific Aim I is influenza vaccination uptake in the ED, **comparing the Intervention M arm vs the Intervention Q arm**. This outcome will be ascertained in the same manner as the primary outcome.

Another secondary outcome for Specific Aim I is Influenza vaccine uptake (at any vaccination location) within 30 days after their index ED visit, comparing the Intervention M arm vs the Control arm. For ascertainment of this outcome, we will:

1) Review of EHR the day after their index visit (as described for the primary outcome ascertainment).
2) Review of EHR at 30 days for receipt of an influenza vaccine.
3) For those who did not get the vaccine in the ED and consent to follow up, we will conduct follow-up phone calls (*Have you received a flu vaccine since your emergency department visit?)* 30 days after index ED visits.

Outcome and Ascertainment of Specific Aim II

Our outcome for Specific Aim II is Influenza vaccine acceptance (defined as a response of "*yes*" to the question "*Would you accept the flu vaccine in the emergency department today if your doctor asked you?*"), comparing the Intervention M arm vs Intervention Q arm. This outcome will be ascertained during the Vaccine Acceptance Survey in both arms.

Outcomes and Ascertainment of Specific Aim III

Our outcome for Specific Aim III is influenza vaccination in the ED, **comparing the** Intervention Q arm (Vaccine acceptance question, but no messaging arm) vs the Control arm (No messaging, no vaccine acceptance question). This outcome will be ascertained in the same manner as the primary outcome of Specific Aim I.

Another outcome for Specific Aim III is Influenza vaccine uptake (at any vaccination location) within 30 days after their index ED visit comparing Intervention Q arm vs Control arms. This outcome will be ascertained in the same manner as the secondary outcome of Specific Aim I.

30 Day phone and EHR Follow-Up

CRCs will only review EHR and conduct phone follow-up with study subjects who have given written consent for these follow-up techniques. CRCs will check the EHR at 2 time periods – the day after their index visit and, if not vaccinated during their ED visit, again 30 days after their visit. CRCs will review Master Data Flow daily (workdays) to determine which subjects have reached the 1-month follow-up time period. By convention, we will use the next month's day that has the same number as the index study visit date, i.e., if the study index visit was on November 5, then the 1-month follow-up should occur on December 5. If December 5 falls on a weekend, then the CRC will use the next study workday (typically the next Monday) as the follow-up date. Study subject's medical record #s and telephone #s will be accessed from the Flu Vaccine Follow up sheet. The CRC who conducts EHR and phone follow-up will be blinded to the subject's study group assignment (intervention vs control arms), i.e., a separate CRC who did not recruit at that site during that day will conduct this phone follow-up.

1) The CRC will first review the EHR to determine whether there is any record of an influenza vaccine received in the preceding time period from the study index visit. If there is a record of vaccination, the CRC will record what date and where the participant received it (if available). See Follow up Data Collection form.
2) If there is no record of vaccination in the EHR, the CRC will proceed with a phone call to the study subject. See Follow up Phone Call Collection form. CRCs will enter follow up data on both the Master Data Flow and Follow up spreadsheets via REDCap links.
    a. If the patient does not answer the phone that morning, the CRC will place two more calls to the study subject over the next 2 workdays. They will vary the time of these calls to improve response.
    b. If the patient does not answer the phone by the third call, the CRC will leave a message with the phone # of the study team. No more calls will be initiated by the study team after this third call.

Data Recording and Entry

CRCs will record survey responses and other data via two mechanisms:

1) Direct entry into the Flu Vaccine Study REDCap database in real time during surveys via secure links
2) Recording onto paper forms first. Then entry of survey information and data after each participant enrollment.

CRCs will keep a running log of all study flow and enrollment, recording the following data for all patients approached: study date, study arm, "Yes" and "No" agreeing to surveys, delivery or non-receipt of messaging platforms, agreeing to receipt of study vaccines, receipt of vaccines in the ED, "Yes" and "No" agreeing to follow-up calls and EHR review. See Master Data Flow.

Data Analysis

Primary Analysis for Specific Aim I

The primary study comparison is uptake (receipt) of an influenza vaccine during their index ED visit, comparing participants seen on Intervention M dates with those seen on Control (No messaging, no vaccine acceptance question) dates to test our study hypothesis: *Implementation of PROFLUVAXED trusted messaging platforms in EDs will be associated with increased Influenza vaccine uptake in unvaccinated ED patients.* This outcome will be ascertained by check of the participant's EHR on the day after their ED visit.

There are two secondary comparisons for Specific Aim I:

1) Influenza vaccination uptake in the ED, comparing the Intervention M arm vs the Intervention Q arm – ascertained by check of the participant's EHR on the day after their ED visit.
2) Receipt of an influenza vaccine within 30 days, comparing participants seen on Intervention M dates with those seen on Control dates - ascertained by check of the participant's EHR on the day after their ED visit and at 30 days.

Outcomes will be compared using mixed logistic regression with a fixed effect for randomization assignment, a normally distributed random effect to allow for clustering by enrolling center, and restricted cubic splines to allow for secular trends during the study period. The treatment effects will be tested by the coefficient for the fixed effect of study arm along with 95% confidence intervals.

Analysis for Specific Aim II

For Specific Aim II, we will compare outcomes in participants seen on Intervention M arm dates with those seen on Intervention Q arm dates to test our study hypothesis: *Implementation of PROFLUVAXED trusted messaging platforms in EDs will be associated with increased influenza vaccine acceptance in unvaccinated ED patients.*

The outcome is Influenza vaccine acceptance (defined as a response of "*yes*" to the question "*Would you accept the flu vaccine in the emergency department today if your doctor asked you?*"). This outcome will be compared using mixed logistic regression with a fixed effect for randomization assignment, a normally distributed random effect to allow for clustering by enrolling center, and restricted cubic splines to allow for secular trends during the study period. The treatment effects will be tested by the coefficient for the fixed effect of study arm along with 95% confidence intervals.

Analysis for Specific Aim III

For Specific Aim III, the outcome is uptake (receipt) of an influenza vaccine during their index ED visit. We will compare outcomes in participants seen on Intervention Q arm dates with those seen on Control dates to test our study hypothesis: *Implementation of an ED protocol in which patients are asked whether they will accept an influenza vaccine (and notifying ED providers*

when they say they will accept it) will be associated with increased influenza vaccine uptake in unvaccinated ED patients.

An additional outcome is receipt of an influenza vaccine within 30 days.

Subgroup Analyses

Another focus of this research is on ED patients who lack primary care group, defined on the Intake survey question: "*Do you have a regular clinic or doctor for medical care?"* We will analyze outcomes according to the binary indicator of having primary care – *yes* vs *no* (and *unsure*).

We will additionally stratify outcomes by study site (representing different regions of the country and different communities), age, gender, primary language, and race/ethnicity.

Subgroups will be tested by adding a subgroup by intervention interaction to the mixed logistic regression. A subgroup will be considered significant if the pairwise intervention by subgroup omnibus test is significant at the 0.05 level.

Rationale for time (1-day unit) cluster and consideration of Alternative Study Designs:

In the study Overview, we described our rationale for switching from a one-week unit to a one-day unit cluster. Our primary goal with this research is to determine whether real-world implementation of influenza vaccine messaging as an ED-site level intervention results in greater acceptance and uptake of influenza vaccines in vulnerable ED populations. Each site sees approximately 150-250 patients per day and applying or not applying the intervention (delivery of influenza vaccine messaging) *for individual patients* in this high workflow, rapid patient turnover ED environment is simply impractical. Given that influenza vaccine messaging may be seen and received by all patients non-selectively in the EDs, patient level randomization would result in high risk of cross-contamination between intervention and control arms. Therefore, removal of the messaging intervention from the site completely during specified time periods (1-day units) of Intervention Q, and removal of both interventions (messaging and the vaccine acceptance question) during Control days is the optimal approach. Although single switches of turning on the interventions at each site (i.e., stepped-wedge trial design) is easier to enact, changes in general population attitudes over time introduce bias that limit the validity of this trial method. We expect gradually increasing acceptance and uptake of the influenza vaccine over time, which would introduce substantial bias toward the intervention. Finally, cost considerations and feasibility limit the number of sites in this trial, negating the potential advantages of a cross-over trial with randomization by sites. These practical and methodological benefits of the 1-day unit cluster RCT far outweigh the smaller sample size and easier analysis with an individual patient unit RCT or a stepped-wedge design.

Statistical approach: In terms of statistical approach, this is a superiority trial in which we seek to verify our central study hypothesis that provision of flu vaccine messaging will result in greater acceptance and uptake of the flu vaccine. Following the recommendations of Hussey and Hughes, our statistical analyses will focus on comparing the vaccine uptake rates during the time periods when influenza vaccine messaging is in place (Intervention Q) and when the

system is not in place (Control - usual care) using mixed effects logistic models. The outcome of interest is the binary indicators of whether they have received a flu vaccine in the ED (uptake - yes/no). Models will include a normally distributed random center effect (on the logit scale) to accommodate potential within-center characteristics (e.g., case mix, demographics), as well as terms for time and intervention. Hypotheses testing will focus on the statistical significance of the intervention indicator. We will fit the mixed effects models using maximum likelihood and routines in Stata.

We will test our primary hypotheses and analyze outcomes according to the study arm (index visit in Intervention Q day vs Control day) to which patients were allocated, regardless of whether they received Influenza vaccine messaging or not - ***intention to treat analysis***.

In addition to the effects on *total* vaccine acceptance, we will also examine the effect of Influenza vaccine messaging on acceptance in patient sub-groups, especially African American and Latinx persons. Influenza vaccine messaging may work for one patient sub-group and not others - these additional analyses will guide future directions and modifications of influenza vaccine messaging.

Sample Size Considerations

The sample size calculations for this research are governed by hypothesis testing of Specific Aim I -- *Implementation of influenza messaging platforms will be associated with increased influenza vaccine uptake in unvaccinated ED patients.* Considering the high benefit of increasing vaccine uptake and the negligible risk of the intervention (a trusted messaging program), even a small effect size of increased uptake would be a clinically important difference. By investigator consensus, we have determined that the intervention would be clinically useful if it increased influenza vaccine uptake by 7%.

We base the sample size calculation on the comparison of the proportion of patients who accept the vaccine between the Intervention M and Control time periods using standard formulae for individual randomization. We have verified that these sample sizes are conservative by simulation of data using a mixed random effects model. Our baseline level of vaccine uptake in the Control arm is estimated to be approximately 5%. With this uptake level we find that at an alpha=0.05 level and a power of at least 0.80, we will need to enroll 744 participants (248 in each arm) in the study to detect the difference of interest (a setting in which the vaccine acceptance rate will increase by 7% during Intervention periods vs Control 2 periods).

We must emphasize that this is a pragmatic trial intended to be completed during a single influenza vaccination season. Enrollment in this study will simply not make sense after March 2023. Carry-over of the study into a second influenza vaccination season (7 months later) would introduce significant confounders (differences in perceptions about influenza vaccines from year to year, influence of different stages of the COVID-19 pandemic**). We therefore will terminate the study at the end of the influenza *vaccination* season (as determined by the PI in consultation with the San Francisco [and other] Departments of Public Health), regardless of enrollment numbers.**

Sample Size for Specific Aim II

From our previous work in the PROCOVAXED study, we expect a baseline vaccine rate (Yes answer to "*Would you accept the flu vaccine in the emergency department today if your doctor asked you?")* of approximately 10%. With the same other assumptions of Specific Aim I (an alpha=0.05 level and a power of at least 0.80), we will need to enroll 1119 participants (373 in each arm) in the study to detect the difference of interest (a setting in which the Influenza vaccine acceptance rate will increase by 7% during Intervention M periods vs Intervention Q periods.

As per above, however, this is a pragmatic trial with a sample size that is governed by Specific Aim I and the intention to complete the study during a single influenza vaccination season. We will terminate the study at the end of the influenza *vaccination* season (as determined by the PI in consultation with the San Francisco [and other] Departments of Public Health), regardless of enrollment numbers.

Sample Size for Specific Aim III

Under the same assumptions of Specific Aim I (baseline uptake rate of 5%, an alpha=0.05 level and a power of at least 0.80), we will need to enroll 744 participants (238 in each arm) in the study to detect the difference of interest (a setting in which the Influenza vaccine uptake rate in the ED will increase by 7% during Intervention Q periods vs Control periods.

As per above, however, this is a pragmatic trial with a sample size that is governed by Specific Aim I and the intention to complete the study during a single influenza vaccination season. We will terminate the study at the end of the influenza *vaccination* season (as determined by the PI in consultation with the San Francisco [and other] Departments of Public Health), regardless of enrollment numbers.

Data management plan

We will manage data using REDCap, hosted by the core site (UCSF) for secure data entry and management. Patient identifiers (medical record numbers and phone numbers) only link will be to unique study ID numbers, which will be housed in files that are kept separate from other study data. We will develop a detailed data dictionary to ensure consistent standards across sites. We will reduce missing or erroneous data using the REDcap data quality tool.

Consents and Rationale

We will obtain scripted verbal consent for Intake surveys in the same manner that we have conducted with the PROCOVAXED study, which is nearly identical in design and scope. We will obtain written HIPAA consent for EHR review and separate written consent for 30-day follow-up phone calls.

With regards to consent for delivery of the messaging intervention, we must emphasize that messaging for vaccine hesitancy is firmly a part of standard best-practice emergency department care (messaging of this type is currently be enacted in EDs across the US). Delivery of the vaccine messaging platforms is therefore an accepted common best practice not requiring consent. To add an extra layer of consent could lead to even greater vaccine hesitancy. We therefore plan the following processes with verbal assent for the Intervention:

1) At the end of the Intake Survey, asking patients if they are willing to watch an influenza vaccine messaging video(s). If the patient says *Yes*, then we will play the video. If the patient says *No*, we will not play the video.
2) Asking participants whether they are willing to read an informational flyer about Influenza vaccines. If the patient says *Yes*, then we will give them the glyer. If the patient says *No*, we will not give them the flyer.
3) Handing the participant's ED provider(s) the scripted message about influenza vaccines to deliver to the participant. Research staff will not mandate or check with providers whether they deliver the message.